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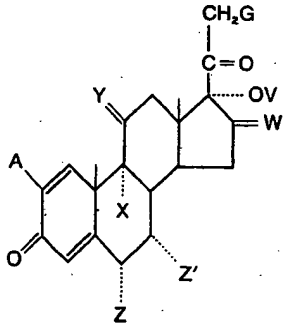
(71) Applicant: SCHERING CORPORATION, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US)

(72) Inventor: Shapiro, Elliot L., 24 Brookshire Drive, Cedar Grove New Jersey 07009 (US)

(74) Representative: Antony, Fritz, Dr. et al, P.O. Box 601 Winkelriedstrasse 35, CH-6002 Lucerne (CH)

(54) Aromatic heterocyclic esters of steroids, their preparation and pharmaceutical compositions containing them.

(57) Disclosed herein are novel 3,20-dioxo-1,4-pregnadiene-17-01-17-aromatic heterocyclic carboxylates (and the 6-dehydro and 1,2-dihydro derivatives thereof) of general formula I:



(I),

wherein:

A is hydrogen or, provided that Y is (H,βOH), A may also be chloro, fluoro or methyl;

X is hydrogen or a halogen atom having an atomic weight less than 100;

Y is oxygen, (H,βOH) or, provided that X is hydrogen, Y may also be (H,H) or, provided X is chloro or bromo, Y may also be (H,β-halogen), the β-halogen having an atomic weight less than 100 and being at least as electronegative as X;

Z is hydrogen, methyl, chloro or fluoro;

Z' is hydrogen or, provided that Z is hydrogen, may also be halogen having an atomic weight of less than 100;

V is an acyl radical of a thiophenecarboxylic acid, pyrrolecarboxylic acid or furancarboxylic acid or the methyl- or halogen-substituted derivatives thereof;

W is (H,H), (H, lower alkyl) or (H, αOV$_1$) where V$_1$ is hydrogen or specified acyl radicals, or W is a methylene or substituted methylene group; and

G is hydrogen, a halogen atom having an atomic weight of less than 100 or is –QV$_2$ where Q is oxygen or sulfur and V$_2$ is specified acyl radicals.

The novel compounds exhibit anti-inflammatory activity and their use for this purpose is disclosed. Also disclosed are methods for the preparation of the novel compounds.

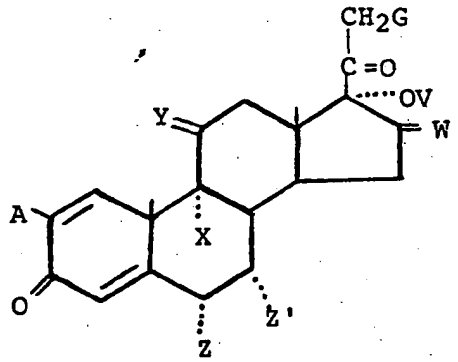
EP 0 057 401 A1

AROMATIC HETEROCYCLIC ESTERS OF STEROIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.

This invention relates to novel aromatic heterocyclic esters of steroids, to their preparation and to pharmaceutical compositions containing them.

More specifically, this invention relates to novel 3,20-dioxo-1,4-pregnadiene-17α-ol 17-aromatic heterocyclic carboxylates, and the 1,2 -dihydro and 6-dehydro derivatives thereof, useful in the treatment of inflammatory conditions.

The novel 17-aromatic heterocyclic carboxylates of this invention are 3,20-dioxo-1,4-pregnadienes of the following formula I:



(I),

wherein A is hydrogen or, provided Y is (H,βOH), A may also be chloro, fluoro or methyl;

X is hydrogen or a halogen atom having an atomic weight less than 100;

Y is oxygen, (H,βOH) or, provided that X is hydrogen, Y may also be (H,H) or, provided that X is chloro or bromo,

—— Y may also be (H,β-halogen) the β-halogen having an atomic weight of less than 100, and being at least as electronegative as X;

Z is hydrogen, CH_3, chloro or fluoro, and Z' is hydrogen or, provided that Z is hydrogen, Z' may also be a halogen atom having an atomic weight less than 100;

V is an acyl radical of thiophenecarboxylic acid, pyrrolecarboxylic acid or furancarboxylic acid or the methyl- or halogen-substituted derivatives thereof;

W is (H,H), (H, lower alkyl) or (H,αOV_1) where V_1 is hydrogen or an acyl radical of retinoic acid or a carboxylic acid having up to 12 carbon atoms; or W is =CHT where T is hydrogen, lower alkyl, fluoro or chloro;

G is hydrogen, a halogen atom having an atomic weight less than 100, or QV_2 where Q is an oxygen or sulfur atom and V_2 is as defined for V or V_1 or is an acyl radical of phosphoric acid which may be in the form of a mono- or di-alkali metal or an alkaline earth metal salt thereof;

and the 6-dehydro and 1,2-dihydro derivatives of the foregoing.

The term 'lower alkyl' as used herein means such groups having up to six carbon atoms and includes straight- and branched-chain groups. Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, n-pentyl, isopentyl, n-hexyl, and 2,3-dimethylbutyl.

The acyl radicals of the aromatic heterocyclic carboxylic acids specified in the definition of V in formula I are those derived from 2-furancarboxylic acid, 3-furancarboxylic acid, 2-thiophenecarboxylic acid, 3-thiophenecarboxylic acid, 2-pyrrolecarboxylic acid, 3-pyrrolecarboxylic acid, and the methyl-and halogen-substituted derivatives thereof such as 5-methyl-2-thiophenecarboxylic acid, N-methyl-2-pyrrolecarboxylic acid, and 5-bromo-2-furancarboxylic acid. Preferred 17-esters are the 17-furoyl and 17-thenoyl esters.

The acyl radicals specified in the definition of V_1 in formula I are those derived from carboxylic acids having up to 12 carbon atoms, which acids may be saturated, unsaturated, straight-chain or branched-chain, aliphatic, cyclic, cyclic-aliphatic, aromatic, aromatic heterocyclic, aryl-aliphatic, or alkyl-aromatic, and may be substituted by hydroxy or by alkoxy or alkylthio containing from 1 to 5 carbon atoms or by a halogen. Exemplary of such acyl radicals are those derived from alkanoic acids exemplified by formic, acetic, propionic, trimethylacetic, butyric, isobutyric, valeric, isovaleric, caproic, tert.-butylacetic, enanthic, caprylic, capric, cyclopentylpropionic, undecylic, lauric, and adamantane-carboxylic acids; substituted alkanoic acids such as phenoxy-acetic, trifluoroacetic, and β-chloropropionic acids; aromatic and substituted aromatic acids, especially benzoic acids substituted by a halogen atom or a methoxy group, such as benzoic, toluic, p-chloro-benzoic, p-fluorobenzoic p-methoxybenzoic, and 3',5'-dimethylbenzoic acids; aromatic-heterocyclic acids in particular iso-nicotinic acid; aryl-alkanoic acids such as phenylacetic, phenylpropionic, and β-benzoylaminoisobutyric acids; unsaturated acids such as acrylic and sorbic acids; and dibasic acids such as succinic, tartaric, phthalic and benzene disulfonic acids.

The preferred acyl groups are those derived from lower alkanoic acids having up to 8 carbon atoms, in particular from acetic, propionic, butyric, valeric, caprylic, caproic and t-butylacetic acids, and from benzoic acid or the substituted benzoic acids mentioned above as well as the corresponding C1-5 alkoxy and alkylthio derivatives of the foregoing acyl groups in particular methoxyacetyl and methylthioacetyl.

Preferred 21-O-ester functions are the 21-acetate and the 21--methoxyacetate and preferred 21-thiol-21-esters are the 21--thiol lower alkanoates and lower alkoxy alkanoates, in particular the 21-thiol-21-pivalate.

The alkylidene groups represented by =CHT are preferably

lower alkylidenes, i.e. hydrocarbon radicals having preferably up to four carbon atoms including radicals such as methylene, ethylidene,n-propylidene, isopropylidene, n-butylidene, and sec.-butylidene and the like.

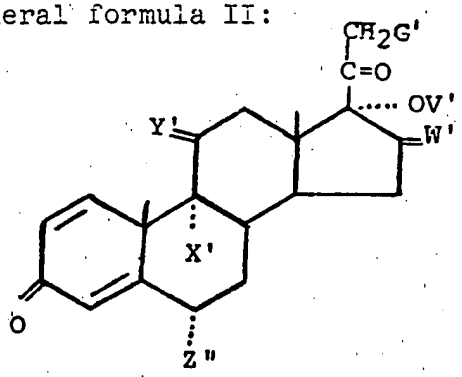
The 3,20-dioxo-1,4-pregnadiene-17α-ol 17-aromatic heterocyclic carboxylates of formula I are usually white to off-white crystalline solids, which are insoluble in water (with the exception of alkali metal salts of esters such as the hemisuccinate and phosphate esters thereof) and soluble in most organic solvents, particularly in acetone, dioxan, dimethylformamide, and dimethylsulfoxide, although of limited solubility in non-polar solvents such as dialkyl ethers and alkylhydrocarbons.

In general, the 3,20-dioxo-1,4-pregnadiene-17α-ol-17-aromatic heterocyclic carboxylates of formula I, particularly those wherein G is QV_2 where V_2 is hydrogen or an acyl group as previously defined, exhibit corticosteroid activity. Those that have halogens at both C-9 and C-11 or an oxygen or β-hydroxyl function at C-11 and a halogen or hydrogen at C-9 possess glucocorticoid activity and are particularly valuable as anti-inflammatory agents.

Particularly useful topical anti-inflammatory agents are the 17-furoyl and 17-thenoyl esters of formula I wherein G is halogeno or QV_2, and C-2 and C-7 are unsubstituted, especially those compounds substituted at C-16 by a lower alkyl group (particularly a 16-methyl group, e.g. 16α-methyl) which generally exhibit topical anti-inflammatory activity superior to the topical anti-inflammatory activity of the 17-non-heterocyclic-carboxylate derivatives corresponding to formula I.

The 17-acyloxy-21-desoxy-derivatives of formula I, while exhibiting anti-inflammatory activity, are generally more valuable as progestational agents.

A preferred group of 3,20-dioxo-1,4-pregnadiene-17α-ol 17-aromatic heterocyclic carboxylates exhibiting particularly useful anti-inflammatory activity can be represented by the general formula II:



(II),

wherein X' is fluoro or chloro;

Y' is (H, βOH) or, provided that X' is chlorine, Y' may also be (H,β-halogen), the β-halogen having an atomic weight of less than 100 and being at least as electronegative as X';

Z" is hydrogen or fluoro;

W' is (H, H) or (H, CH_3);

V' is furancarbonyl or thiophenecarbonyl; and

G'is chloro or fluoro, or QV_2', wherein Q is sulfur or preferably oxygen and V_2' is hydrogen or an acyl radical of retinoic acid, of carboxylic acids having up to 12 (preferably up to 8) carbon atoms or of phosphoric acid and which may be in the form of a mono- or di-alkali metal or alkaline earth metal salt.

Preferred compounds include the 17-(2'-furoate), 17-(3'-furoate), 17-(2'-thenoate) and the 17-(3'-thenoate) ester derivatives of the following:

9α,11β,21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol--3,20-dione;

9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol--3,20-dione 21-acetate;

9α-chloro-(and the corresponding 9α-fluoro-)16α-methyl--1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate;

9α-chloro-(and the corresponding 9α-fluoro-)21-chloro--16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione;

as well as the following 21-analogs of the foregoing: 21-fluoro-, 21-methoxyacetate and 21-thio-21-pivalate. The 6α-fluoro-derivatives of the foregoing also represent a preferred area of the compounds of the general formula I, of which may be mentioned:

6α-fluoro-9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-acetate, and

6α-fluoro-9α,11β,21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate).

Other compounds which may be specifically referred to are the 16-unsubstituted analogs of the foregoing compounds as well as the 16β-methyl epimers thereof.

Of the foregoing, particularly valuable are 9α,11β,21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate) and 9α,21-dichloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione-17-(2'-furoate) and 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) which have high topical and local anti-inflammatory activity.

Further compounds of the formula I which may be mentioned are:

1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate,

16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate,

1,4,6-pregnatriene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate,

4-pregnene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate,

16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione-17-(2'furoate) 21-acetate,

7α-chloro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate;

21-desoxy pregnadienes (i.e. compounds of formula I wherein G is hydrogen) such as:

9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate),

9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-furoate),

9α-fluoro-16-methylene-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'furoate) 21-acetate, and

9α-fluoro-1,4-pregnadiene-11β,16α,17α,21--tetrol-3,20-dione 17-(2'-furoate) 16,21-diacetate.

The present invention also provides a process for the preparation of the 17α-aromatic heterocyclic carboxylates of the invention, which process comprises subjecting an appropriate 3,20-dioxo-1,4-pregnadiene starting material, or a 6-dehydro or 1,2-dihydro derivative thereof, to one or more of the following general methods A to D, namely:

A: introduction of the desired ester group at the 16α,17α and/or 21 positions, or

B: hydrolysis of an ester group present at one or more of positions 11, 16α and 21 or of a 16α,17α-or 17α,21 ortho ester group, or

C: halogenation at one or more of positions 9α,11β and 21, or

D: reduction of an 11-oxo group to an 11β hydroxy group.

General Method A

The 17α-aromatic heterocyclic carboxylates of the present invention may conveniently be prepared by a process of general method A above, the process comprising esterification of a corresponding 17α-ol starting material having present in the molecule the other desired substituents. This method is particularly applicable to the preparation of those preferred compounds of the formula I where X is chloro and Y is (H,β-Cl) —— or where X is fluoro and Y is (H,β-OH) and G is an acyloxy group as specified in the definition of $-QV_2$; that is for

the preparation of specified 17α,21-diesters of the general formula I.

Typically, reaction is effected by esterifying a 17α-hydroxy-21-acylate starting material with the required aromatic heterocyclic carboxylic acid, usually in the form of a reactive derivative of the acid such as an acid halide (e.g. acid chloride)or acid anhydride in the presence of a basic catalyst preferably a 4-dialkylaminopyridine such as 4-dimethylaminopyridine.

The 17α-esterification is preferably carried out under conditions which minimise undesirable side-reactions, such as hydrolysis of other ester functions present in the molecule. Thus, the use of aqueous or alcoholic media is generally to be avoided, the reaction being preferably effected in a non-reactive organic solvent under anhydrous conditions. Examples of suitable non-reactive organic solvents are acetonitrile, tetrahydrofuran, pyridine, dimethylformamide and, as a preferred solvent, methylene chloride. While esterification may be effected at any convenient temperature, it is preferred to use room temperature, that is about 20°C. The reaction is usually complete in 24 to 120 hours depending upon the nature of the reactants and the reaction conditions used.

Prior to esterification of the 17α-hydroxy group, any desired free 11β-hydroxy (or 16α-hydroxy) function present in the molecule of the starting material is desirably protected in known manner with a suitable protecting group which, after esterification at C-17, is then removed.

17α,21-Diesters falling within the scope of the present invention may alternatively be prepared by 21-acylation of a corresponding 21-hydroxy-17α-ester starting material with the appropriate acid, usually in the form of a reactive derivative, such as the acid anhydride or acid chloride, and preferably in the presence of a tertiary base such as pyridine. Any desired free hydroxy group at C-11 or C-16 may be suitably protected as mentioned above.

A 21-dihydrogenphosphate ester may be prepared by reaction

of the corresponding 21-hydroxy compound with pyrophosphoryl chloride. The mono-and di-alkali metal salts and alkaline earth metal salts of the dihydrogen phosphate ester may be obtained by partial or complete neutralisation with an alkali metal methoxide or alkaline earth metal methoxide.

Esterification at C-17 is also a convenient method for preparing those compounds of the invention where X is hydrogen, Y is an oxygen atom and G is an acyloxy group as specified in the definition of $-QV_2$. Following esterification at C-17, the 11-oxo group may, if desired, be reduced to give further, an 11β,17α,21-triol 17,21-diacylate of the present invention.

Those compounds of the invention where W in position 16 of formula I is (H, O-acyl) as specified in the definition of $-OV_1$, that is 16α- esters of the general formula I, may be prepared by esterification of a corresponding 16α-hydroxy group in a similar manner to that specified for esterification at C-21, any free hydroxy group at C-11 or C-21 being protected as necessary.

General Method B

17α-Acyloxy-21-hydroxy compounds of the present invention may be prepared by a process of general method B above, the process comprising 21-deacylation of a corresponding 17α,21-ester. The hydrolysis step is typically effected under acid conditions using strong mineral acid, preferably 70% perchloric acid in methanol. Where it is desired to deacylate an 11β- and/or 16α-ester function present in the molecule of the starting material, this may similarly be effected using appropriate hydrolysis conditions known in the art.

17α-Acyloxy-21-hydroxy compounds of the invention, as well as 17α-acyloxy-16α-hydroxy compounds, may also be prepared by hydrolysis of a corresponding 17α,21-orthoester or 16α,17α-orthoester respectively. The hydrolysis may be effected under mildly acidic conditions, e.g. in the presence of a lower alkanoic acid (e.g. acetic or propionic acid) or a strong mineral acid (e.g. hydrochloric or sulphuric acid).

The orthoester starting materials may be prepared in known manner by reacting the appropriate diol, for instance the corresponding 17α,21-diol, with a trialkyl heterocyclic orthoester, such as 2-trimethyl-orthothenoate, 2-trimethyl-orthofuroate or 2-trimethyl-orthopyrroloate, in an appropriate organic solvent (e.g. a dioxan -benzene mixture) in the presence of a catalyst (e.g. pyridinium p-toluene sulfonate).

General method B also encompasses the hydrolysis, as a last step, of an 11β- and/or 16α-protected hydroxy group using appropriate hydrolysis conditions known in the art to give the desired compound of the formula I. The method may suitable be used for the preparation of 17α,21-diesters of the general formula I.

General Method C

A further general method for the preparation of the compounds of the invention, designated above as method C, comprises halogenation at one or more of positions 9α,11β and 21. This method is particularly applicable to the preparation of those preferred compounds of the general formula I where G is halogen, in particular chloro or fluoro, or an acyloxy group as specified in the definition of $-QV_2$, and X is chloro and Y is (H,βCl) or X is chloro or fluoro and Y is (H,βOH).

Thus, where a 9α,11β-dichloro compound of the general formula I is required a 9(11)-dehydro-starting material bearing all the other desired structural variants may be treated with chlorine in a halogenated solvent (e.g. carbon tetrachloride) in the presence of a tertiary amine such as pyridine.

For the preparation of a 21-halogeno compound of the invention, a corresponding 21-sulfonate, such as a 21-mesylate or 21-tosylate, or a comparable ester, may be treated with a suitable source of the desired halogen ion, for instance with a tetraalkyl ammonium halide (e.g. chloride or fluoride) or alkali metal halide preferably with lithium chloride where a 21-chloro compound is requried. The reaction may typically

be effected by heating the reactants in a suitable solvent, for instance dimethylformamide. This method is primarily applicable to those compounds of the formula I where X is fluoro and Y is (H,β-OH) or where X is chloro and Y is (H,β-OH).

9α,11β,21-Trihalogeno compounds of the invention are preferably prepared by 21-halogenation followed by 9α,11β-halogenation.

9α-Halogeno-11β-hydroxy compounds, in particular 9α-chloro-11β-hydroxy compounds, of the invention may be prepared from a corresponding 9(11)-dehydro starting material by reaction with a suitable halogenating agent such as an N-chloro-amide, preferably 1,3-dichloro-5,5-dimethylhydantoin, and a strong mineral acid, preferably perchloric acid, in an inert organic solvent such as moist dioxan or tetrahydrofuran.

Alternatively, the 9α-halogeno-11β-hydroxy compounds of the general formula I may be prepared by treating a corresponding 9β,11β-oxido-starting compound with hydrogen chloride or hydrogen fluoride in a suitable inert solvent. Thus, for instance, the 9α-chloro-11β-hydroxy compounds of the general formula I (which represent a preferred group of compounds) may be prepared by treating a corresponding 9β,11β-oxido-compound, preferably at room temperature, with anhydrous hydrogen chloride in a suitable inert medium, such as glacial acetic acid.

21-Halogenation with concomitant introduction of the desired 17-aromatic heterocyclic ester group may be achieved by treating a 17α,21-aromatic heterocyclic orthoester with a triarylsilyl halide (such as a tritolylsilyl or triphenylsilyl halide) or a tri-lower alkylsilyl halide (such as a trimethylsiyl halide) in known manner as described, for instance - in USP 3,992,422.

General Method D

A further general method for the preparation of 11β-hydroxy-17α-aromatic heterocyclic carboxylates of the present invention comprises reduction at the 11 position of a corresponding 11-oxo-17α-ester. This method is particularly applicable to the preparation of 11β-hydroxy-17α-aromatic heterocyclic carboxylate 21-acylates of the invention. Reduction may be effected in known manner, typically by treating an 11-oxo-17α,21-diester starting material with a suitable reducing agent including sodium, potassium or lithium borohydride, tetra-n-butylammonium borohydride or lithium tri-t-butoxy-aluminium hydride, in an inert solvent, preferably sodium borohydride in an inert organic solvent such as dimethylformamide. Usually, reduction will be effected at somewhat reduced temperatures at or about 0°C.

The foregoing methods A to D are illustrated in the following specific examples, primarily by reference to the preparation of 3,20-dioxo-1,4-pregnadienes of the present invention. By use of the appropriate starting materials, however, the corresponding 3,20-dioxo-4-pregnenes and 3,20-dioxo-1,4,6-pregnatrienes may similarly be prepared. In preparing, by the foregoing methods A to D, the compounds of the formula I bearing a substituent at one or more of positions 2,6,7 and 16, that substituent may conveniently be present in the starting material employed in the foregoing methods.

EXAMPLE 1

9α, 11β-DICHLORO-16-METHYL-1,4-PREGNADIENE-17α,21-DIOL-3,20-DIONE 17-HETEROCYCLIC CARBOXYLATE 21-ALKANOATES

A) 9α,11β-Dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-acetate

Dissolve 4-dimethylaminopyridine (12 gms.), 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate (4.8 gms.) and 2-furoyl chloride (2 ml.) in methylene chloride (62 ml.) and stir at room temperature until thin-layer chromatography of a portion of the mixture indicates that no more of the desired product is being formed. Evaporate the reaction mixture, add an excess of dilute hydrochloric acid to the resultant residue, stir for 30 minutes and collect the insolubles. Add an excess of dilute sodium carbonate, stir for 30 minutes, collect the solids, wash with water, and dry at 60°C. to obtain 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-acetate.

Purify the crude product by recrystallizing from methylene chloride (75 ml.)/ether (300 ml.). Further purify by clarifying a methylene chloride solution of this recrystallized product by gravity filtration through charcoal (Darco G-60), then again recrystallizing the product by adding ether (200 ml.) to the methylene chloride solution adjusted to 45 ml. after Darco treatment) and concentrating to 200 ml. Add an additional 50 ml. of ether, filter off the crystals, and dry at 45°C. under vacuum to obtain the purified product $[\alpha]_D^{26}$+65.7°(dioxan); λmax. 245nm (ε 23,060); theory (percent) C 61.8, H 5.72; found C 61.84,

H 5.57.

B) 9α,11β-Dichloro-16β-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-acetate

Treat 9α,11β-dichloro-16β-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate in a manner similar to that described in Example 1A, first paragraph, to obtain the title compound.

Purify the crude product by preparative thin-layer chromatography on silica gel, using chloroform:ethyl acetate (19:1) as the developing solvent. Visualize the desired band by ultraviolet light, remove the band, and elute with ethyl acetate. Evaporate the solvent and recrystallize from methylene chloride:ether to obtain purified 9α,11β-dichloro-16β-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-acetate: λmax 245nm (ε 23,340); 252nm (ε 22,990); mass spectrum (no parent ion): 491, 490, 489, 379, 351, 349, 279, 277, 95, 43.

C) 9α,11β-Dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-heterocyclic carboxylate 21-acetates

Similarly, by substituting 3-furoyl chloride, 2-thenoyl chloride, and 5-bromo-2-furoyl chloride for 2-furoyl chloride in Example 1A, first paragraph, there are obtained 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(3'-furoate) 21-acetate: λmax. 237nm (ε 17,600); mass spectrum (no parent 563ion): (491, 489) 279, 121, 95, 43;
9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-thenoate) 21-acetate: λmax. 241 nm (ε 22,900), inflexion 270nm; mass spectrum (no parent ion): 507, 506, 505, 380, 349, 279, 111, 43;
and 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-[2'-(5'-bromofuroate)] 21-acetate: mass spectrum: (no parent ion) 569, 567, 469, 467, 452, 451, 450, 424, 351, 350, 349, 173, 43.

Each product had been purified by the preparative thin-layer chromatographic method described in Example 1B, second paragraph; followed by recrystallisation of the resultant residues from ethyl acetate:hexane, methylene chloride: hexane, and ethyl acetate:hexane, respectively

D) 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-propionate

Treat 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 21-propionate with 2-furoyl chloride in the manner of Example 1A, first paragraph, to obtain the title compound.

Purify the resultant crude product as in Example 1B, second paragraph, to obtain purified 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-propionate: λmax 244nm (244-258nm broad) (ε 23,000); mass spectrum (no parent ion) 491, 489, 371, 353, 351, 331, 315, 313, 279, 277, 95, 57.

EXAMPLE 2

9α,11β,21-TRICHLORO-16-METHYL-1,4-PREGNADIENE-17α-OL-3,20-DIONE 17-HETEROCYCLIC CARBOXYLATES

A) 16-Methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17-heterocyclic carboxylate 21-acetates

1) Dissolve 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (9.96 gms., 25 mmols.), 2-furoyl chloride (4.95 ml., 50 mmols.), and 4-dimethylaminopyridine (30.35 gms., 250.0 mmols.) in methylene chloride (150 ml.) and stir at room temperature until thin-layer chromatography of an aliquot of the reaction

mixture indicates that no more product is being formed. Evaporate the mixture and treat the residue with dilute hydrochloric acid and then with sodium carbonate as in Example 1A. Dissolve the collected insolubles in acetone (300 ml.) and add to a saturated sodium chloride solution to precipitate 16α-methyl-1,4,9(11)-pregnatriene-17α, 21-diol-3,20-dione 17-(2'-furoate) 21-acetate.

Purify by chromatography on silica gel, eluting with chloroform:ethyl acetate (9:1). Combine like fractions as determined by thin-layer chromatography and evaporate to obtain the purified product.

2) Treat 16β-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate in the manner of Example 2A(1) to obtain 16β-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-acetate.

3) Substitute 3-furoyl chloride and 2-thenoyl chloride for 2-furoyl chloride in Example 2A(1) to obtain 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17-(3'-furoate) 21-acetate and 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17-(2'-thenoate) 21-acetate, respectively.

B) <u>16-Methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17-heterocyclic carboxylates</u>

1) To a suspension of the compound prepared in Example 2A(1) (4.46 gms.) in methanol (125 ml.) at room temperature, add 70% perchloric acid (4.9 ml.), dropwise. Let stand overnight. Filter off any insolubles; add the filtrate to a saturated sodium chloride solution, collect the solids and dry them at 45°C. to obtain 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17-(2'-

furoate).

2) Hydrolyze each of the 17-heterocyclic carboxylate 21-acetates of Example 2A(2) and (3) in a similar manner to obtain the corresponding 17-heterocyclic carboxylate 21-hydroxy compounds.

C) 16-Methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17-heterocyclic carboxylate 21-mesylates

1) To a solution of the compound prepared in Example 2B (1) (3 gms.) in pyridine (43 ml.) cooled to 0-2°C., add dropwise mesyl chloride (5.1 ml.) and let stand for one hour. Pour the reaction mixture into ice water and collect and dry the resultant precipitate to obtain 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-mesylate.

2) To a solution of the 16β-methyl compound prepared in Example 2B(2) (0.361 gm.) in pyridine (4 ml.) cooled to 0-5°C., add dropwise mesyl chloride (0.62 ml.) and let stand for one hour. Pour the reaction mixture into a saturated sodium chloride solution, collect the resultant precipitate and dry it at 60°C. to obtain 16β-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-mesylate.

3) Treat each of the 17-(3'-furoate) and 17-(2'-thenoate) compounds prepared in Example 2B(2) in a manner similar to that described in Example 2C(1) to obtain the corresponding 17-heterocyclic carboxylate 21-mesylates.

D) 21-Chloro-16-methyl-1,4,9(11)-pregnatriene-17α-ol-3,20-dione 17-heterocyclic carboxylates

1) Stir the product of Example 2C(1) (3.4 gms.) and lithium chloride (3.4 gms.) in dimethylformamide (51 ml.) at 80°C. for 9 hours. Add the reaction mixture to a saturated sodium chloride solution, collect the resultant precipitate and dry it at 50°C. to obtain 21-chloro-16α-methyl-1,4,9(11)-pregnatriene-17α-ol-3,20-dione 17-(2'-furoate).

2) Treat the product of Example 2C(2) in a similar manner to that described in Example 2D(1) to obtain 21-chloro-16β-methyl-1,4,9(11)-pregnatriene-17α-ol-3,20-dione 17-(2'-furoate). Purify this product by preparative thin-layer chromatography on silica gel using chloroform: ethyl acetate (19:1) as developing solvent. Visualize the desired band with ultraviolet light, remove the band and elute with ethyl acetate. Evaporate the solvent to obtain the purified product.

3) Treat each of the compounds prepared in Example 2C(3) in a manner similar to that described in Example 2D(1).

Purify the resulting crude 21-chloro-16α-methyl-1,4,9(11)-pregnatriene-17α-ol-3,20-dione 17-(3'-furoate) by recrystallisation from methylene chloride:hexane, followed by preparative thin-layer chromatography using chloroform: ethyl acetate (8:1) as the developing solvent.

Purify the crude 21-chloro-16α-methyl-1,4,9(11)-pregnatriene-17α-ol-3,20-dione 17-(2'-thenoate) as in Example 2D(2), second paragraph.

E) <u>9α,11β,21-Trichloro-16-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-heterocyclic carboxylates</u>

1) To a solution of the product of Example 2D(1) (2.3 gms.,

4.0 mmols.) and pyridine hydrochloride (1.42 gm.) in methylene chloride (37 ml.) at -35°C. to -40°C. add carbon tetrachloride containing chlorine (3.26 ml.; 128 mgs. Cl_2 per milliliter) and stir for 20 minutes. Evaporate the solvent, add water to the resultant residue, and collect the insolubles to obtain 9α, 11β, 21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate).

Purify the product by recrystallization from methylene chloride:ether, followed by preparative thin-layer chromatography on silica gel using chloroform:ethyl acetate (9:1) as the developing solvent. Visualize the desired band with ultraviolet light, remove the band and elute with ethyl acetate. Evaporate the solvent to obtain the purified product: λmax 245.5nm (ε 24,300), shoulder 253 nm; theory (percent) C 60.08, H 5.41, Cl 19.71; found C 60.37, H 5.49, Cl 19.59.

2) In a manner similar to that described in Example 2E(1), treat each of the products of Example 2D(2), (3) and (4) with chlorine in carbon tetrachloride to obtain the corresponding 9α,11β,21-trichloro 17-heterocyclic carboxylates, i.e., 9α,11β,21-trichloro-16β-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate); 9α,11β,21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(3'-furoate): λ max 236 nm (ε 16,300); theory (percent) C 60.06, H 5.41; found C 59.77, H 5.29 ; and 9α, 11β, 21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-thenoate): λ max 240 nm (ε 22,390); theory (percent) C 58.33, H 5.26, Cl 19.13; found C 57.90, H 5.10, Cl 19.34.

EXAMPLE 3

9α-FLUORO-16-METHYL-1,4-PREGNADIENE-11β,17α,21-TRIOL-3,20-DIONE 17-HETEROCYCLIC CARBOXYLATES

A) 9α-Fluoro-16-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17-heterocyclic carboxylate 21-acetates

1) To a solution of 4-dimethylaminopyridine (8.4 gms., 70 mmols.) in methylene chloride (42 ml.), add dropwise 2-furoyl chloride (1.8 ml., 18.2 mmols.) with stirring. Add 9α-fluoro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (3 gms., 6.9 mmols.) and stir at room temperature until thin-layer chromatography of a portion of the reaction mixture indicates that no more product is being formed. Evaporate the reaction mixture and treat the resultant residue by successive trituration with dilute hydrochloric acid and with dilute sodium carbonate; collect the insolubles, wash with water, and dry under vacuum at 40°C. to obtain 9α-fluoro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17-(2'-furoate) 21-acetate.

Purify the crude product by preparative thin-layer chromatography on silica gel: develop the plates twice in chloroform:ethyl acetate (40:1), visualize the desired band by ultraviolet light, remove the band and elute with ethyl acetate. Evaporate the eluate to a residue to obtain purified 9α-fluoro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17-(2'-furoate) 21-acetate.

2) In the procedure of Example 3A(1), substitute for 2-furoyl chloride equivalent amounts of 3-furoyl chloride and 2-thenoyl chloride to obtain 9α-fluoro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17-(3'-furoate) 21-acetate and 9α-fluoro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17-(2'-thenoate) 21-acetate, respectively.

3) Treat 9α-fluoro-16β-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate in a manner similar to that

described in Example 3A(1), first paragraph, but substitute dimethylformamide:methylene chloride (1:1) for methylene chloride.

Purify the crude 9α-fluoro-16β-methyl-1,4-pregnadiene-17α, 21-diol-3,11,20-trione 17-(2'-furoate) 21-acetate as in Example 3A(1), second paragraph, followed by a second preparative thin-layer chromatographic purification using hexane:ethyl acetate (2:1) as the developing solvent.

B) 9α-Fluoro-16-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-heterocyclic carboxylate 21-acetates

1) To a solution of the compound prepared in Example 3A(1) (0.986 gm., 1.866 mmol.) in dimethylformamide (26 ml.), methanol (30 ml.) and water (3 ml.), cooled to 0-2°C. under an atmosphere of nitrogen, add solid sodium borohydride (0.212 gm., 5.56 mmols.). After 20 minutes, add 1 N hydrochloric acid (6 ml.), wait 1 minute, and pour the reaction mixture into a saturated sodium chloride solution (600 ml.). Collect the precipitate and dry it at 60°C.

Purify the crude product by preparative thin-layer chromatography on silica gel, using chloroform:ethyl acetate (9:1) to develop the plates. Visualize the desired band by ultraviolet light, remove the band, and elute with ethyl acetate. Evaporate the solvent and recrystallize the resultant residue from methylene chloride:ether to obtain 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate; λ max 247 nm (ε 25,890); theory (percent) C 65.89, H 6.29, F 3.59; found C 65.92, H 6.23, F 3.58.

2) In the procedure of Example 3B(1) first paragraph,

substitute the products of Example 3A(2) for the 17-(2'-furoate), substitute argon for nitrogen, and run at 0-5°C. to obtain 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(3'-furoate) 21-acetate and 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-thenoate) 21-acetate, respectively.

Purify the crude 17-(3'-furoate) and 17-(2'-thenoate) by preparative thin-layer chromatography as in Example 3B(1), second paragraph, substituting chloroform:ethyl acetate at ratios of (19:1) and (13:1) for the developing solvents, respectively to obtain the purified 17-(3'-furoate): λ max 237 nm (ε 16,700); $[\alpha]_D^{26}$ +9.0° (dioxan); mass spectrum (no parent ion): 508, 456, 455, 397, 396, 395, 279, 278, 215, 187, 112, 95, 43; and the purified 17-(2'-thenoate) λ max 242nm(ε 22,310), 270 nm (inflexion) (ε 11,373); mass spectrum (no parent ion): 524, 471, 315, 295, 277, 128, 111, 73, 43.

3) To a solution of the compound prepared in Example 3A(3) (26 mgs., 0.0494 mmols.) in methanol (2.5 ml.) and water (0.3 ml.), cooled to 0-5°C. under a nitrogen atmosphere, add sodium borohydride (7 mgs., 0.148 mmol.). After 20 minutes, add to dilute hydrochloric acid and extract with ethyl acetate to obtain 9α-fluoro-16β-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate.

Purify the crude product using preparative thin-layer chromatography as in Example 3B(1), second paragraph, substituting chloroform:ethyl acetate (19:1) for the developing solvent to obtain the purified product: λ max 248 nm (ε 25,500); mass spectrum (no parent ion): 508, 455, 396, 315, 295, 277, 112, 95, 43.

C) 9α-Fluoro-16-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-heterocyclic carboxylates

1) To a suspension of the compound prepared in Example 3B(1) (334 mgs., 0.634 mmols.) in methanol (9 ml.) under an atmosphere of nitrogen, add with stirring 70% perchloric acid (0.34 ml.). After 18 hours separate the insolubles and add the clear reaction mixture to a saturated aqueous sodium chloride solution (150 mls.); collect the precipitate and dry it at 60°C. to obtain 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate).

2) Treat the compound prepared in Example 3B(3) in a manner similar to that described in Example 3C(1) to obtain 9α-fluoro-16β-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate).

Purify the crude product by recrystallization from ethyl acetate:hexane, then by preparative thin-layer chromatography in the usual manner, using chloroform:ethyl acetate (4:1) as developing solvent.

3) In the procedure of Example 3C(1) substitute for the 17-(2'-furoate) equivalent amounts of 17-(3'-furoate) and 17-(2'-thenoate) to obtain the corresponding 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(3'-furoate) and 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-thenoate).

D) 9α-Fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-propionate

1) To a solution of the compound of Example 3C(1) (0.1 gm. 0.021 mmol.) in pyridine (3 ml.) cooled to 0-2°C., add

propionyl chloride (0.3 ml., 0.035 mmol.). After 17 hours, add to dilute hydrochloric acid and extract with ethyl acetate. Evaporate the ethyl acetate extract to give a residue comprising 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-propionate.

Purify the crude product by preparative thin-layer chromatography using chloroform:ethyl acetate (8:1) as developing solvent, followed by recrystallization from methylene chloride:hexane; λmax 246 nm (ε 26,300); mass spectrum (no parent ion) 522, 457, 456, 455, 427, 374, 315, 295, 277, 95, 57.

2) In the procedure of 3D(1), treat the products of Examples 3C(2) and (3) with propionyl chloride to obtain the corresponding 17-heterocyclic carboxylate 21-propionates.

EXAMPLE 4

9α-FLUORO-21-CHLORO-16-METHYL-1,4-PREGNADIENE-11β, 17α-DIOL-3,20-DIONE 17-HETEROCYCLIC CARBOXYLATES

A) 9α-Fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-heterocyclic carboxylate 21-mesylates

1) Dissolve the compound of Example 3C(1) (269 mgs., 0.553 mmol.) in a mixture of mesyl chloride (0.43 ml., 5.53 mmol.) and pyridine (2.75 ml.) maintained at 0-2°C. After 1 hour, add the reaction mixture to a saturated sodium chloride solution. Collect the insoluble material and dry it at 40°C. to obtain 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate)

21-mesylate.

2) In a similar manner to Example 4A(1), treat the compounds prepared in Examples 3C(2) and (3) to obtain the corresponding 17-heterocyclic carboxylate 21-mesylates.

B) 9α-Fluoro-21-chloro-16α-methyl-1,4-pregnadiene-11β, 17α-diol-3,20-dione 17-heterocyclic carboxylates

1) Dissolve the compound of Example 4A(1) (279 mgs., 0.494 mmol.) and lithium chloride (350 mgs.) in dimethylformamide (4 ml.) and maintain the temperature at 80°C. for 21 hours. Add the reaction mixture to a saturated sodium chloride solution, collect the insolubles and dry at 50°C. to obtain 9α-fluoro-21-chloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-furoate).

Purify the product by preparative thin-layer chromatography using chloroform:ethyl acetate (8:1) as developing solvent. Recrystallize the resultant chromatographic extract from methylene chloride:hexane to obtain the purified title compound: λ max 247 nm (ε 26,210); theory (percent) C 64.22, H 5.99. found C 64.13, H 5.66.

2) Treat the compounds prepared in Example 4A(2) in the manner of Example 4B(1) to obtain the corresponding 21-chloro 17-heterocyclic carboxylate, i.e., 9α-fluoro-21-chloro-16β-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-furoate): λ max 248 nm (ε 24,800); mass spectrum (no parent ion): 486, 485, 484, 374, 373, 372, 317, 316, 315, 297, 296, 295, 95, 43; 9α-fluoro-21-chloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(3'-furoate): λ max 238 nm (ε 18,400); max spectrum (no parent ion): 484, 372, 295, 277, 95; and 9α-fluoro-21-chloro-

16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-thenoate): λ max 243 nm (ε 24,460), inflexion at 260 and 272 nm; theory (percent) C 62.24, H 5.80, S 61.5, F 3.65; found C 62.07, H 5.73, S 6.59, F 3.53.

EXAMPLE 5

1,4-PREGNADIENE 11β,17α,21-TRIOL 3,20-DIONE 17-(2'-FUROATE) 21-ACETATE AND ITS 9α-FLUORO DERIVATIVE

A) 1,4-Pregnadiene-17α,21-diol-3,11,20-trione 17-(2'-furoate) 21-acetate

Treat 1,4-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate in a manner similar to that described in Example 1A, first paragraph, to obtain the title compound.

Purify the product by successive preparative thin-layer chromatography procedures, the first using chloroform: ethyl acetate (9:1) as developing solvent, the second using hexane:ethyl acetate (2:1).

B) 1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate

To a solution of the compound of Example 5A (148 mg.) in methanol (15 ml.), dimethylformamide (10 ml.), and water (1.5 ml.), cooled to 0-2°C. under a nitrogen atmosphere, add sodium borohydride (34.1 mgs.). After 20 minutes, add to dilute hydrochloric acid (250 ml.) and collect the insolubles. Extract the aqueous solution with ethyl acetate, evaporate the organic phase and combine the residue and insolubles to give 1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate.

Purify the crude product by preparative thin-layer chromatography in the usual manner using chloroform:ethyl acetate (4:1) as the developing solvent, followed by recrystallizing from methylene chloride:hexane to obtain the purified product: λmax 249 nm (ε 26,510); mass spectrum (no parent ion): 496, 384, 283, 265, 250, 237, 223, 95, 43.

C) 9α-Fluoro-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate

Treat 9α-fluoro-1,4-pregnadiene-17α,21-triol-3,11,20-trione 21-acetate with 2-furoyl chloride and purify the product as described in Example 5A. Reduce the 17-(2'-furoate) thus prepared with sodium borohydride and purify as described in Example 5B to produce the title compound.

EXAMPLE 6

16-METHYL-1,4-PREGNADIENE-11β,17α,21-TRIOL-3,20-DIONE 17-(2'-FUROATE) 21-ACETATES

Treat each of 16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate and 16β-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate in a manner similar to those of Examples 5A and 5B to obtain the corresponding 16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate and 16β-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate.

EXAMPLE 7

9α,11β-DICHLORO-16α-METHYL-1,4-PREGNADIENE-17α,21-DIOL-3,20-DIONE 17-(5'-METHYL-2'-THENOATE) 21-ACETATE

Dissolve 4-dimethylaminopyridine (3 gms.), 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate (1 gm.), and 5-methyl-2-thenoyl chloride (0.6 ml.) in methylene chloride (10 ml.) and stir at room temperature until thin-layer chromatography of a portion of the mixture indicates no more of the desired product is being formed. Dilute the resultant mixture with methylene chloride (200 ml.), add dilute hydrochloric acid and stir for 45 minutes. Separate the methylene chloride phase, wash it with dilute sodium carbonate and then with water, and evaporate the organic phase.

Purify the crude product by preparative thin-layer chromatography on silica gel using chloroform:ethyl acetate (40:1) as developing solvent. Visualize the desired band by ultraviolet light, remove the band, and elute with ethyl acetate. Repeat the preparative thin-layer chromatography, developing with chloroform:ethyl acetate (15:1). Elute with ethyl acetate, evaporate the solvent, and recrystallize the resultant residue from methylene chloride:ether to obtain pure 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(5'-methyl-2'-thenoate) 21-acetate: λ max 241 nm (ε 20,570), 277 nm (ε 14,100); mass spectrum (no parent ion): 519, 349, 279, 126, 125, 43.

EXAMPLE 8

9α-FLUORO-16α-METHYL-1,4-PREGNADIENE-11β,17α,21-TRIOL-3,20-DIONE 17-(5'-METHYL-2'-THENOATE) 21-ACETATE

Treat 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate in a manner similar to that described in Example 7, first paragraph, but with the addition of 2.5 ml. dimethylformamide, to obtain the title compound.

Purify the crude product by preparative thin-layer chromatography as usual, developing with chloroform:ethyl acetate (50:1). Purify further by preparative thin-layer chromatography using chloroform:ethyl acetate (10:1) as developing solvent and recrystallize the resultant residue from methylene chloride:hexane to give a purified product: λ max 244 nm (ε 21,770), 277 nm (ε 13,450); mass spectrum (no parent ion): 487, 485, 374, 343, 316, 315, 296, 125, 43.

EXAMPLE 9

9α,11β-DICHLORO-16α-METHYL-1,4-PREGNADIENE-17α,21-DIOL-3,20-DIONE 17-(N-METHYL-2'-PYRROLYL-CARBOXYLATE) 21-ACETATE

Dissolve 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α, 21-diol-3,20-dione 21-acetate (3 gms.) in methylene chloride (30 ml.) and add 4-dimethylaminopyridine (8.4 gms.) and N-methylpyrrole-2-carbonyl chloride (2 ml.). Stir at room temperature until thin-layer chromatography of a portion of the mixture indicates that no more of the desired product is being formed. Evaporate the reaction mixture, add dilute sodium carbonate, and stir 1 hour. Extract the solution three times with 200 ml. methylene chloride, combine the organic phases, wash them with water, and evaporate them to a residue to obtain the title compound.

Purify the crude compound by silica gel chromatography, eluting with ethyl acetate. Combine like fractions as determined by thin-layer chromatography, and evaporate the solvent to obtain the title compound. Purify further by preparative thin-layer chromatography, using chloroform: ethyl acetate (20:1) as developing solvent. Extract the

sample band as usual with ethyl acetate, evaporate, and recrystallize the resultant residue from ether to obtain the pure title compound: mass spectrum (no parent ion): 502, 279, 277, 271, 142, 108, 43.

EXAMPLE 10

6α-FLUORO-16α-METHYL-1,4-PREGNADIENE-17α-OL-3,20-DIONE 17-AROMATIC HETEROCYCLIC CARBOXYLATES

A) 6α-Fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate

1) 6α-Fluoro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17-(2'-furoate) 21-acetate

Dissolve 4-dimethylaminopyridine (9 gms.) and 2-furoyl chloride (2.1 ml.) in methylene chloride (40 ml.), add 6α-fluoro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (2.9 gms.) in methylene chloride (20 ml.) and stir at room temperature for 96 hours. Dilute the reaction mixture with methylene chloride (300 ml.), then wash with dilute hydrochloric acid. Separate the organic phase, dry it over anhydrous sodium sulfate, and evaporate it to a residue.

Dissolve the resultant residue in methylene chloride (100 ml.) and filter the solution through neutral aluminium oxide to obtain the purified title compound. Purify further by preparative thin-layer chromatography using ethyl acetate:hexane (1:1) to develop the plates, extract the band as usual with ethyl acetate, and evaporate the extract to a residue to obtain the purified product.

2) 6α-Fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate

Dissolve the product of Example 10A(1) (0.360 gm.) in dimethylformamide (10 ml.) and methanol (10 ml.). Cool the solution to 0°C., and under a nitrogen atmosphere add sodium borohydride (0.073 gm.). Stir for 30 minutes at 0°C. Add dilute hydrochloric acid (18 ml.) to the reaction mixture and pour the resultant solution into ice water saturated with sodium chloride. Collect the resultant solids and purify by preparative thin-layer chromatography using chloroform:ethyl acetate (2:1) as developing solvent. Extract the product as usual with ethyl acetate, evaporate to a residue, and recrystallize it from ethyl acetate: hexane (3:1) to obtain the purified title compound: λ max 247 nm (ε 27,800); mass spectrum: 528, 455, 315, 112, 95, 43.

B. 6α-Fluoro-9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-acetate

1) 6α-Fluoro-16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate

Under a nitrogen atmosphere, cool to 0°C. a solution of 6α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (12.5 gms.) in dimethylformamide (25 ml.) and collidine (25 ml.). Add slowly methanesulfonyl chloride/SO_2 solution (1.41 gm. CH_3SO_2Cl/ml.) and stir for 45 minutes at 0°C. and then stir for 30 minutes at room temperature. Pour the resultant reaction mixture into ice water (1.1 liter), collect the insolubles and wash these with water to obtain the crude title compound. Dissolve the residue in methylene chloride, filter through silica gel, and evaporate the solvent to obtain the purified product.

2) 6α-Fluoro-16α-methyl-1,4,9(11)-pregnatriene-17α, 21-diol-3,20-dione 17-(2'-furoate) 21-acetate

Treat the product of Example 10B(1) in a manner similar to that described in Example 2A(1), first paragraph, to obtain the title compound. Purify the crude product as usual by preparative thin-layer chromatography, developing with hexane:ethyl acetate (2:1).

3) 6α-Fluoro-9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-acetate

Treat the product of Example 10B(2) in a manner similar to that described in Example 2E(1), substituting hexane:ethyl acetate (2:1) as solvent; and purify further by recrystallizing from methylene chloride:hexane, to obtain the title compound: λmax 243 nm (ε 23,300); mass spectrum (no parent ion): 509, 507, 398, 397, 395, 289, 287, 269, 267, 297, 229, 95, 43.

C) 6α-Fluoro-9α,11β,21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate)

1) 6α-Fluoro-16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17-(2'-furoate)

Treat the product of Example 10B(2) in a manner similar to that described in Example 2B(1) to obtain the title compound. Purify by preparative thin-layer chromatography as usual, using chloroform:ethyl acetate (9:1) to develop the plates, and hexane:ethyl acetate (2:1) to recrystallize the purified title compound.

2) 6α-Fluoro-16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-mesylate

Dissolve the product of Example 10C(1) (4.4 gms.) in pyridine (30 ml.), add mesyl chloride (5 ml.) cooled to 0-2°C., and stir 1 hour at room temperature under a nitrogen atmosphere. Pour the reaction mixture into dilute hydrochloric acid (300 ml.) and collect and dry the insolubles to obtain the title compound.

3) 6α-Fluoro-21-chloro-16α-methyl-1,4,9(11)-pregnatriene-17α-ol-3,20-dione 17-(2'-furoate)

Treat the compound prepared in Example 10C(2) in a manner similar to that described in Example 2D(1) to obtain the title compound.

4) 6α-Fluoro-9α,11β,21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate)

Treat the compound prepared in Example 10C(3) in a manner similar to that described in Example 2E(1) first paragraph, but, rather than evaporating the organic solvent, wash the reaction mixture with water, dry the organic phase over anhydrous sodium sulfate, and evaporate to a residue.

Purify the resultant residue as usual by preparative thin-layer chromatography, using chloroform:ethyl acetate (19:1) to develop the plates and ethyl acetate to extract the product. Recrystallize from methylene chloride:hexane to obtain the purified title compound: λ max 243 nm (ε 23,000), inflexion 255 nm; mass spectrum 556, 521, 510, 509, 507, 481, 479, 317, 95.

D) 6α-Fluoro-9α,21-dichloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-furoate)

Dissolve the compound prepared in Example 10C(3) (0.974 gm.)

in tetrahydrofuran (25 mls.) and cool to 15°C. Add perchloric acid (0.3 ml. of 70% perchloric acid in 0.7 ml. water) and 1,3-dichloro-5,5-dimethylhydantoin (0.237 gm.), and stir under a nitrogen atmosphere at room temperature for 2 hours. Add the reaction mixture to a solution of sodium bisulfite in water (2 gms. in 250 ml.) and collect the solids to obtain the title compound. Purify the crude product by chromatography on silica gel G-60, combine the desired fractions as determined by thin-layer chromatography and evaporate to give the purified product: λ max 245 nm (ε 23,000); mass spectrum (no parent ion): 489, 349, 313, 293, 112, 95, 77, 35.

EXAMPLE 11

9α,11β-DICHLORO-16α-METHYL-1,4-PREGNADIENE-17α,21-DIOL-3,20-DIONE 17-(2'-THENOATE)

A) 9α,11β-Dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17α,21-(2-methylorthothenoate)

Dissolve 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione (2 gms.) in a mixture of dioxan (20 ml.) and benzene (60 ml.) and reflux using a Dean-Stark take-off collector. After distilling off 20 ml. solvent, add 2-trimethylorthothenoate dissolved in benzene (1.82 gm. in 10 ml.) and pyridinium p-toluenesulfonate (0.072 gm.). Reflux for ten minutes with distillation and concurrent replacement of benzene. Repeat the addition of orthoester and pyridinium tosylate and the distillation step four more times.

Cool the reaction mixture to room temperature, add 3 drops of pyridine and evaporate *in vacuo* to a residue comprising the title compound.

B) 9α,11β-Dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-thenoate)

Dissolve the residue prepared in Example 11A in acetic acid (35 ml. of a 90% solution in water) and stir at room temperature for 24 hours. Add the reaction mixture to water (300 ml.) and extract with ethyl acetate to obtain the title compound. Purify the crude material by recrystallization from methylene chloride:hexane and by preparative thin-layer chromatography as usual, using chloroform:ethyl acetate (9:1) as developing solvent to obtain the pure title compound: λ max 241 nm (ε 22,310), inflexions at 251, 258 and 263 nm); mass spectrum (no parent ion): 507, 505, 317, 315, 279, 111, 91, 83.

EXAMPLE 12

9α-FLUORO-16α-METHYL-1,4-PREGNADIENE-11β,17α,21-TRIOL 3,20-DIONE 17-(2'-FUROATE) 21-METHOXY-ACETATE

Cool a solution of 0.115 gm. of 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20 dione 17-(2'-furoate) [prepared in Example 3C(1)] in 1 ml. of pyridine to 5°C. and then add 0.05 ml of methoxyacetyl chloride. After 5 minutes allow the temperature to rise to room temperature and then stand for 75 minutes. Add the reaction mixture to aqueous hydrochloric acid and collect the insoluble material (100 mg). Purify by preparative thin-layer chromatography using a mixture of chloroform:ethyl acetate (2.5:1) to develop the plates, extract the band with ethyl acetate and evaporate the extract to give the title compound (91 mg.; yield 68% of theory). Further recrystallisation may be effected using an ethyl acetate: hexane mixture. Title compound: mass spectrum (no parent ion) 540, 539, 538, 426, 315, 295, 95, 45.

The corresponding 21-methylthioacetate analog of the title compound may similarly be prepared using methylthioacetyl chloride in place of methoxyacetyl chloride.

EXAMPLE 13

9α,11β-DICHLORO-17α,21-DIHYDROXY-16α-METHYL-1,4-PREGNADIENE-3,20-DIONE 17-(2'-FUROATE) 21-METHOXYACETATE

To 5 ml. of pyridine at 0-2°C add with stirring 0.15 ml. methoxyacetyl chloride. To the resulting suspension add 522 mg. of 9α,11β-dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2'-furoate). After 5 minutes allow the temperature of the reaction mixture to rise to room temperature and maintain, under stirring, for 3 hours. Add the product mixture to distilled water, saturate with sodium chloride and then filter off the white precipitate, wash and then dry under vacuum at 50°C. to give 594 mg. of product (theory yield). Recrystallise the crude product twice from a methylene chloride-ether mixture at reflux temperature.

Further purify the product by preparative thin layer chromatography on 1000 micron silica gel plates using chloroform:ethyl acetate (9:1) as developing solvent. Elute the desired band with ethyl acetate, filter the eluant, remove the solvent by evaporation at room temperature and then dry the residue under vacuum at 50°C to give 465 mg. of product (yield 78% of theory). Recrystallise the product from a methylene chloride-hexane mixture at reflux temperature to give white needles of the pure title product (384 mg.; yield 65% of theory): λ max 245nm (ε 23280); mass spectrum: 522, 491, 489, 410, 379, 377, 351, 349, 315, 313, 279, 277, 121, 112, 95.

EXAMPLE 14

9α-21-DICHLORO-11β,17α-DIHYDROXY-16α-METHYL-1,4-PREGNADIENE 3,20-DIONE 17-(2'-FUROATE)

Prepare under nitrogen a solution of 1.80 gms. of 21-chloro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2'-furoate) [obtained in a manner similar to that described in Example 10C(3)] in 39 ml of dry tetrahydrofuran.

Maintain under nitrogen and cool on an ice bath. Add, with stirring, a solution of 1.15 ml of 70% perchloric acid in 2.53 ml of distilled water, and immediately thereafter 604 mg. of 1,3 dichloro-5,5-dimethylhydantoin. Stir the reaction mixture for twenty minutes and then raise the temperature to ambient temperature. Monitor the comsumption of starting material by thin layer chromatography of aliquots using chloroform:ethyl acetate (9:1) and hexane: ethyl acetate (1:1). We found that a sample taken 2 hours after the hydantoin reactant addition indicated total consumption of starting material. At 2.5 hours after hydantoin addition the reaction mixture was poured into 500 ml. of distilled water containing 7 gms. of sodium bisulphite. Sodium chloride was added until the solution was saturated. The precipitated solid was filtered off, washed copiously and then dried at 50°C. under vacuum.

The resulting crude product was purified by preparative chromatography on 1000 micron silica gel plates using chloroform: ethyl acetate (19:1). The desired band was eluted with ethyl acetate, the eluate filtered and then evaporated at room temperature to give 1.3 gm. of product (yield 65% of theory). The product was recrystallised

by dissolving in refluxing methylene chloride, filtering and then replacing the methylene chloride at reflux with methanol and then the methanol with distilled water. Selfseeding occurred. The suspension was cooled to room temperature, filtered and then dried under vacuum at 50°C. to give the pure title product: λ max 247 nm (ε 24,940); mass spectrum (no parent ion) 486, 484, 374, 372, 331, 313, 295, 277, 121, 95.

EXAMPLE 15

9α-CHLORO-21-FLUORO-11β,17α-DIHYDROXY-16α-METHYL-1,4-PREGNADIENE-3,20-DIONE 17-(2'-FUROATE)

A) 21-Fluoro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2'-furoate)

Stir at room temperature a mixture of 1.411 gm. of 21-fluoro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione (made by the procedure of Herz et al., JACS, 78, 4812(1956)), 1.623 gm. of furoic anhydride and 1.923 gm of 4-dimethylamino-pyridine in 16 ml of methylene chloride for 5 days until thin layer chromatography indicates 80-85% reaction. Air-evaporate the methylene chloride, triturate the residue with water and then collect the solid product by filtration. Dry the product at 50°C. under vacuum (yield 1.79 g.). Purify the crude product by preparative thin layer chromatography on 1000 micron silica gel plates using a chloroform:ethyl acetate mixture (first 9:1 and then 19:1 ratio) as developing solvent. Elute the desired band with ethyl acetate, filter the eluate and evaporate at room temperature to give a residue of 1.35 gm. (yield 75.8% of theory). Recrystallise the product twice from methylene chloride to yield white needles of 21-fluoro-17α-hydroxy-16α-methyl-1,4,9(11) pregnatriene-3,20-dione 17-(2'-furoate) (764 mg.;yield 43% of theory): λ max 246.5 nm (ε 25,430); mass spectrum:

452, 437, 340, 325, 307, 279, 224, 171, 95.

B) 9α-Chloro-21-fluoro-11β,17α-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2'-furoate)

To a cooled solution (0-2°C) maintained under nitrogen of 538.5 mg. of the product obtained by Step A in 12 ml. of tetrahydrofuran, add with stirring a solution of 0.36 ml. of 70% perchloric acid in 0.8 ml. of distilled water and immediately thereafter 187.5 mg. of 1,3-dichloro-5,5'-dimethyl-hydantoin. After 5 minutes remove the reaction mixture from the ice bath, discontinue the nitrogen flow and stir the reaction at room temperature for 150 minutes until consumption of the starting material is substantially complete as indicated by thin layer chromatography of aliquots using hexane:ethyl acetate (2:1). Pour the product mixture into 700 ml of distilled water containing 2 gm. of sodium bisulphite. Add sodium chloride until the solution is saturated.

Filter off the precipitate, wash copiously with water and then dry at 60°C under vacuum to give 597 mg. of crude product (yield 96% of theory)

Purify the crude product by preparative thin layer chromatography on 1000 micron silica gel plates using chloroform: ethyl acetate (9:1). Elute the desired band with ethyl acetate, filter the eluate, evaporate off the solvent and then triturate the residue with ether, discarding the supernatant liquor. Dry the product at room temperature (yield 440 mg). Recrystallise from a methylene chloride: hexane mixture at reflux temperature to give 375 mg. of the pure title compound: λ max 246 nm (methanol) (ε 25,730); mass spectrum: 505, 504, 469, 468, 356, 331, 313, 295, 277, 121, 95.

EXAMPLE 16

9α-CHLORO-11β,17α-DIHYDROXY-16α-METHYL-21-THIOL-1,4-PREGNADIENE-3,20-DIONE 17-(2'-FUROATE) 21-PIVALATE

A) 9β,11β-Epoxy-17α-hydroxy-16α-methyl-21-thiol-1,4-pregnadiene-3,20-dione 17-(2'-furoate) 21-pivalate

Prepare a mixture of 236.3 mg. of 9β,11β-epoxy-17α-hydroxy-16α-methyl-21-thio-1,4-pregnadiene-3,20-dione 21-pivalate (prepared according to the procedure of British patent specification 2,037,290A), 206 mg. of furoic anhydride and 244.4 mg. of 4-dimethylamino-pyridine in 2ml. of methylene chloride. Stir the mixture in a stoppered 2 dram vial for 160 minutes at which time the reaction should be substantially complete as indicated by thin layer chromatography of a sample on silica gel plates using as eluant chloroform:ethyl acetate (19:1) and then hexane:ethyl acetate (2:1). Evaporate the product mixture at room temperature and triturate the residue with distilled water. Filter off the insolubles and dry at 60°C. under vacuum.

Purify the crude product by preparative thin-layer chromatography on 1000 micron silica gel plates using as eluant chloroform:ethyl acetate. Extract the desired band with ethyl acetate and evaporate the resulting extracts at room temperature. Recrystallise from a methylene chloride:diethyl ether:hexane mixture to give 229 mg (yield 81% of theory) of 9β,11β-epoxy-17α-hydroxy-16α-methyl-21-thiol-1,4-pregnadiene-3,20-dione 17-(2'-furoate) 21-pivalate: λ max 250 nm (methanol) (ε 30,320); mass spectrum: 566, 538, 454, 435, 323, 295, 121, 112, 95, 85, 57.

B) 9α-Chloro-11β,17α-dihydroxy-16α-methyl-21-thiol-1,4-pregnadiene-3,20-dione 17-(2'-furoate) 21-pivalate

Prepare a suspension of 185 mg. of the product of Step A in 1.5 ml. of glacial acetic acid. Place in a 2 dram vial, chill to 10°C and then add, under stirring, 0.3 ml. of a glacial acetic solution of hydrogen chloride (containing 10.9 mg. of HCl per ml. of acetic acid). Allow the contents of the stoppered vial to return to room temperature and then after 45 minutes pour into distilled water. Filter off the precipitate, wash with water, dilute sodium carbonate solution and then again with water. Dry overnight under air suction to give 185 mg. of crude product.

Purify the crude product by thin layer preparative chromatography on 1000 micron silica gel plates using chloroform:ethyl acetate (19:1) as eluant. Extract the desired band with ethyl acetate, evaporate off the solvent and then extract the residue with a methylene chloride: diethyl ether-hexane mixture. Remove the solvent under air evaporation at room temperature and then dry under vacuum at 50°C. to give 142 mg. (yield 72% of theory) of product. Recrystallise from a methylene chloride: hexane mixture at reflux temperature to give white needles. Dry under vacuum at 50°C to give 101 mg. (yield 52% of theory) of the title compound: λ max 245 nm (methanol) (ε 26,330). The mass spectrum was consistent with the structure of the title compound (molecular weight 603.155) as shown by peak matching; found: m^+566 (corresponding to loss of HCl:36), m^+471 (corresponding to loss of $H_2C.S.CO.t\text{-}Bu$:131).

EXAMPLE 17

9α-CHLORO-11β,17α,21-TRIHYDROXY-16α-METHYL-1,4-PREGNADIENE-3,20-DIONE 17-(2'-FUROATE)-21-METHOXY-ACETATE

Prepare a solution of 480 mg. of 17α,21-dihydroxy-16α-methyl 1,4,9(11)-pregnatriene-3,20-dione 17-(2'-furoate) 21-methoxyacetate in 9 ml. of tetrahydrofuran. Cool to 0-2°C and under nitrogen add with stirring a solution of 0.17 ml. of 70% perchloric acid in 0.42 ml. of distilled water followed immediately thereafter by 127 mg of 1,3-dichloro-5,5-dimethyl-hydantoin. Stir for 5 minutes then remove the ice bath, discontinue the flow of nitrogen and allow the temperature to rise to room temperature. Allow to stand for 2 hours then pour the reaction mixture into an aqueous sodium bisulfite solution (1.4 gm. of $NaHSO_3$ in 400 ml. of distilled water). Add sodium chloride to saturation. Filter off the solid product, wash with distilled water, partially air dry and then complete drying at 60°C. under vacuum.

Purify the crude product by preparative thin layer chromatography on 1000 micron silica gel plates using chloroform:ethyl acetate (4:1) as eluant. Extract the desired band with ethyl acetate, filter the extract, evaporate off the solvent and then dry the residue at 60°C. under vacuum to give 240 mg. of product. Recrystallise from aqueous acetone at reflux temperature to give fine needles of the pure title product (yield 207 mg.): λ max 247 nm (ε 25,680); mass spectrum (no parent ion(538, 473, 471, 443, 435, 426, 407, 389, 363, 365, 333, 331, 315, 313, 295, 277, 121, 95.

EXAMPLE 18

9α-CHLORO-11β,17α,21-TRIHYDROXY-16α-METHYL-1,4-PREGNADIENE 3,20-DIONE 17-(2-FUROATE) 21-ACETATE

Treat 615.6 mg. of 17α,21-dihydroxy-16α-methyl-1,4,9(11) pregnatriene-3,20-dione 17-(2'-furoate) 21-acetate in a similar manner to that described in Example 17 to give, after purification, 256 mg. (yield 37.6% of theory) of the pure title compound: λ max 247 nm (ε 26,820); mass spectrum —— 545,544, 473, 471, 333, 331, 315, 313, 295, 279, 277, 95, 43.

Alternatively, prepare the title compound using the procedure described in Example 16.

EXAMPLE 19

9α-FLUORO-16α-METHYL-11β,17α,21-TRIOL-1,4-PREGNADIENE-3,20-DIONE 17-(2'-FUROATE) 21-ACETATE

A) 9α-Fluoro-16α-methyl-11β,17α,21-triol-1,4-pregnadiene-3,20-dione 11β-trifluoracetate 21-acetate

Prepare a solution of 1.36 gm. of trifluoroacetic anhydride in 10 ml. of pyridine. Add 5 ml. of this reagent, chilled to 0-2°C, to a chilled solution of 434.5 mg. of dexamethasone acetate in pyridine. Stir for 15 minutes and then pour the resulting dard green solution into 200 ml. of 3.6 N. sulfuric acid solution.

Filter off the green solid, wash with water, resuspend it in water, stir, filter again, wash and then dry under vacuum at room temperature. The crude product was purified by preparative chromatography on 1000 micron silica gel plates using chloroform:ethyl acetate (9:1). The desired area was extracted with ethyl acetate, the extract filtered and then evaporated at room temperature. The crude product was solidified with diethyl ether and hexane and then dried at 50°C under vacuum to give the title compound (198 mg; yield 37% of theory).

B) 9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 11β-trifluoracetate 17-(2'-furoate) 21-acetate

In a manner similar to that described in Example 2A treat, in methylene chloride, 150 mg. of the product of Step A with a reaction mixture of 2-furoyl chloride and 4-dimethylaminopyridine, stirring the reaction mixture for 66 hours. Dilute the reaction mixture with methylene chloride, wash with water, then 1N HCl followed by dilute sodium carbonate solution and then water adjusted to pH 5-6. Dry the methylene chloride solution over magnesium sulfate, filter and then air evaporate to give a residue of 162 mg. Purify by chromatography on 1000 micron silica gel plates using chloroform:ethyl acetate as eluant as described in Example 2A. Dissolve the product on diethyl ether filter and then evaporate. Dry at 50°C under vacuum to give 50 mg. of product.

C) 9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2'-furoate) 21-acetate

Treat 21 mg. of the product of step B with 72 mg. of sodium benzoate in 2 ml. of methanol for 3 hours under stirring. Pour the reaction mixture into saturated aqueous sodium chloride solution. Filter off the white precipitate, wash with water and then dry at room temperature .

Purify by treating with diethyl ether:hexane to give 25 mg. of the title product which is identical to the product obtained in Example 3B(1) by reduction of a corresponding 11-ketone.

EXAMPLE 20

9α,21-DICHLORO-11β,17α-DIHYDROXY-16α-METHYL-1,4-PREGNADIENE-3,20-DIONE 17-(2'-FUROATE)

A) 21-Chloro-9β,11β-epoxy-17α-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione

Prepare a solution of 5.0 g. of 9β,11β epoxy-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione in 20 ml. of dry pyridine. Cool on an ice bath; to the stirred solution under nitrogen, add dropwise 1.1 ml of mesyl chloride. Remove the ice bath and continue stirring at room temperature for 30 minutes. Add 2.0 gm. of lithium chloride and continue stirring for a further 150 minutes. Add to a mixture of 150 ml ethyl acetate and 100 ml distilled water in a separating tunnel. Wash the organic phase with dilute 3% aqueous hydrochloric acid, then saturated aqueous sodium chloride solution and finally saturated aqueous sodium bicarbonate solution. Dry the organic phase over magnesium sulfate, filter and remove the solvent. Recrystallise from methylene chloride:diethyl ether to give from the combined crops 4.62 gm. of the title compound.

B) 21-Chloro-9β,11β-epoxy-17α-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2'-furoate)

Prepare under argon a solution of 8 gm. of 4-dimethyl-amino-pyridine in 250 ml of dry methylene chloride. Cool on an ice bath and add to the stirred solution 6.0 ml of 2-furoyl chloride. Remove from the ice bath, allow the temperature to rise to room temperature and then add 11.5 gm. of the product of Step A. After 24 hours add under rapid stirring 500 ml. of ethyl acetate saturated with water. Filter off the precipitate and then evapo-

rate off the solvent from the filtrate to give the crude title product which was used without further purification in Step C.

C) 9α,21-Dichloro-11β,17α-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2'-furoate)

To the product of Step B add 50 ml. of glacial acetic acid. To the stirred solution under argon, then add a solution of 3.5 gm. of anhydrous hydrogen chloride in 125 ml. of glacial acetic acid. Stir for 15 minutes and then quench with 500 ml. of distilled water. Filter off the solids, recrystallise from methanol: water, dry for 24 hours under vacuum to give 12.6 gm. of the title compound (yield 83% of theory) essentially identical with the prodduct obtained in Example 14.

Using the procedures described in the foregoing Examples, the following compounds of the general formula I may be prepared:

a) 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-butyrate: λ max 245 nm (ε 23,600) 245-258 nm (broad); mass spectrum (no parent ion): 491, 489, 373, 371, 351, 349, 331, 279, 95, 91, 43;

b) 9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-butyrate: λ max 247 nm (ε 26,390); mass spectrum (no parent ion): 536, 456, 455, 315, 295, 95, 71;

c) 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate):

λ max 243 nm (ε 20,910) (inflexions at 247, 251 and 256 nm); mass spectrum (no parent ion); 491, 489, 351, 349, 315, 279, 95;

d) 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(3'-furoate:
λ max 236 nm (ε 17,400) (inflexions at 255, 262 and 268 nm); mass spectrum (no parent ion): 491, 489, 410 408, 389, 379, 377; 351, 349, 338, 306, 279, 95;

e) 9α,11β,21-trichloro-16β-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate):
λ max 245 nm (ε 23,420), 254 nm (ε 22,950); mass spectrum (no parent ion): 491, 489, 351, 349, 315, 313, 279, 277, 95;

f) 9α,11β-dichloro-21-fluoro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate):
λ max 245 nm (ε 22,760); mass spectrum (no parent ion): 488, 486, 451, 390, 376, 374, 351, 349, 340, 325, 315, 313, 279, 277, 95;

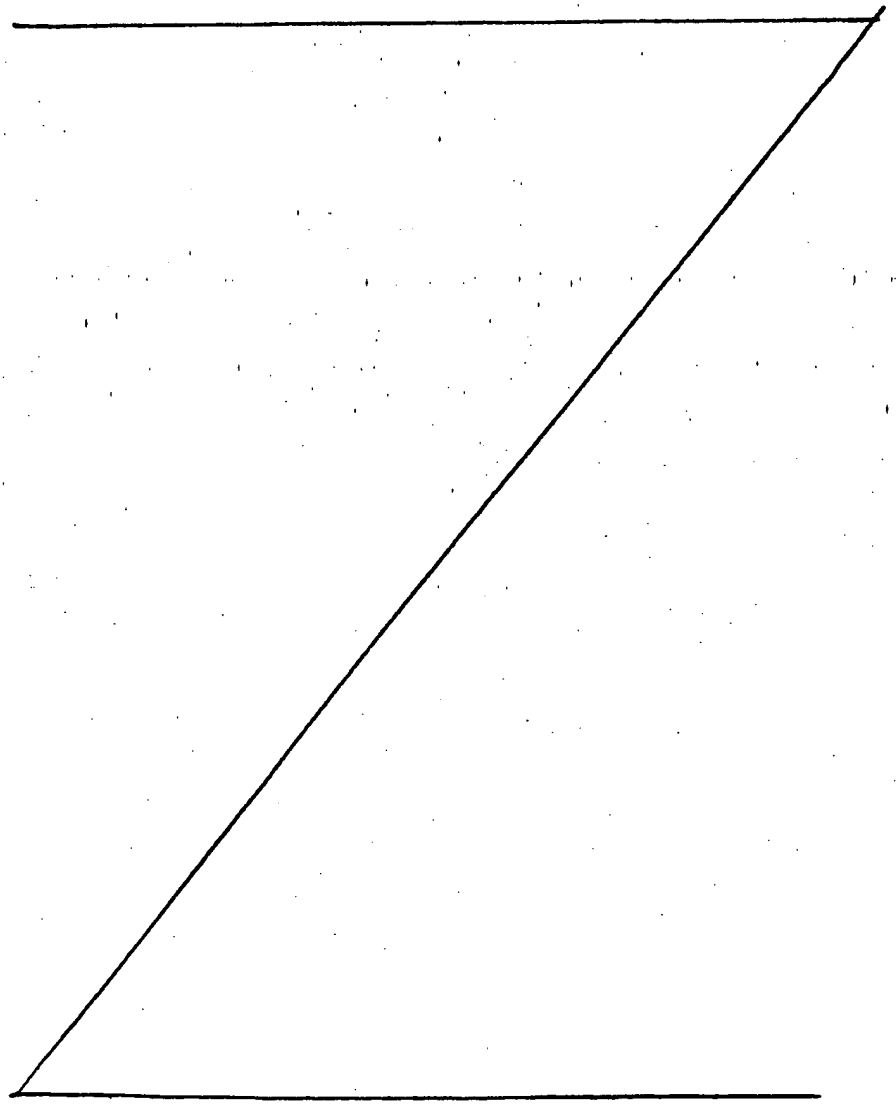
g) 9α-fluoro-16-methylene-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate :
λ max 245 nm (ε 25,270); mass spectrum 526, 506, 415 313, 112, 95;

h) 9α,21-dichloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-thenoate):
λ max 243 nm (ε 23,500) (inflexions at 262 and 272); mass spectrum (no parent ion): 502, 500, 451, 423, 295, 111, 91;

i) 9α-chloro-16-methylene-1,4-pregnadiene-11β,17α, 21-triol-3,20-dione 17-(2'-furoate) 21-acetate:

λ max 246 nm (ε 24,370); mass spectrum 542, 506, 469, 431, 295, 293, 111, 95; and

j) 9α-fluoro-21-chloro-16α-methyl-1,4-pregnadiene-17α-ol-3,11,20-trione 17-(3'-furoate):
λ max 237 nm (ε 18,570); mass spectrum 504, 502, 453, 425, 405, 281, 96, 95.



As previously mentioned, the compounds of the general formula I exhibit useful corticosteroid activity, in particular useful anti-inflammatory activity. Representative 3,20-dioxo-1,4-pregnadiene-17α-ol 17-aromatic heterocyclic carboxylates of the general formula I have been found to exhibit unexpectedly enhanced anti-inflammatory activity compared with known high-potency reference steroidal esters. Thus, when tested in mice by a modification of the well-known 5-day croton oil ear edema tests (B.N. Lutsky, et. al., Arzneim.-Forsch. 29, 992, 1979), 9α,11β,21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate) exhibited topical potency about eight times that of the well known topical anti-inflammatory agent betamethasone 17-valerate.

In another of its aspects the invention provides pharmaceutical compositions suitable especially for the treatment of inflammatory conditions in animals and humans and comprising a compound of the general formula I together with a suitable pharmaceutical carrier. In general, the compounds of the formula I may be formulated in a manner similar to that for the corresponding known 17-alkanoates .

For topical or local administration the compounds of the formula I may be in the form of creams, lotions , aerosols, ointments or powders in the treatment of all corticosteroid responsive dermatoses such as contact and allergic dermatitis, eczemas and psoriasis or may be in the form of ophthalmic suspensions or nasal sprays.

Ointments and creams may be formulated in conventional manner with an aqueous or oily base with the addition of suitable thickening and/or gelling agents.

Lotions, similarly, may be formulated with an aqueous or oily base and may include in conventional manner stabilizing agents, emulsifying agents, dispersing agents, suspending agents, thickening agents, coloring agents, perfumes and the like.

Powders may be formulated using any suitable powder base, e.g. talc, lactose, starch, etc. Drops may be formulated with an aqueous base or non-aqueous base also comprising one or more dispersing agents, suspending agents, solubilizing agents, etc.

The pharmaceutical compositions may include one or more preservatives or bacteriostatic agents.

The compositions may also contain other active ingredients such as antimicrobial agents, particularly antibiotics.

The proportion of active steroid in the compositions according to the invention depends on the precise type of formulation to be prepared but will generally be within the range of from 0.0001% to 5% by weight. Generally, however, for most types of preparations advantageously the proportion used will be within the range of from 0.001 to 0.5% and preferably 0.01 to 0.25%.

The daily dosage of the indicated pharmaceutical composition will, as for compositions containing the corresponding 17-alkanoates, be determined by the attending physician and will depend upon such factors as the nature and severity of the inflammation being treated, the age and size of the patient and the specific potency of the formula I compound being administered.

The following examples illustrate topical formulations in accordance with the invention. In each, a preferred active ingredient is:

9α,11β,21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate); however, this compound may be replaced by equivalent quantities of other compounds of the formula I, such as:

9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17-(2'-furoate) 21-acetate,

9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17- (2'-furoate)21-acetate, and

9α-fluoro-21-chloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-furoate), and

9α-21-dichloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-furoate).

FORMULATION EXAMPLES

1. Glycol Ointment

	mg/g
Active ingredient	0.1-5.0
Hexylene Glycol	100.0
Propylene Glycol Monostearate	20.0
White Wax	60.0
White Petrolatum to make	1.00 g

Melt and heat together to 60-65°C. the propylene glycol monostearate, white wax and white petrolatum. Heat the hexylene glycol to 40°C. and dissolve the active ingredient in it. Add, with agitation, the solution of the hexylene glycol to the above oily phase (cooled to 55°C). Cool, with agitation, until the temperature reaches 30°C.

2. Lotion

	mg/g
Active ingredinet	0.1-5.0
Ethyl alcohol	400.0
Polyethylene Glycol 400	300.0
Hydroxypropyl Cellulose	5.0
Propylene Glycol to make	1.0 g

Dissolve the active ingredient in the mixture of the ethyl alcohol, polyethylene glycol and propylene glycol. Slowly add the hydroxypropyl cellulose and continue to agitate until the hydroxypropyl cellulose is completely despersed and wetted and a clear lotion is produced.

3. Cream

	mg/g
Active ingredient	0.1-5.0
Isopropyl Palmitate	100.0
Glyceryl Stearate	80.0
Promulgen-Type D (Robinson, Wagner Co.)	50.0
White Wax	50.0
Propylene Glycol	100.0
Purified water to make	1.00 g

Melt together and heat to 75°C the white wax, glyceryl stearate, Promulgen-Type D and a portion of the isopropyl palmitate and maintain the temperature. Disperse the active ingredient in the remaining portion of the isopropyl palmitate and mill the dispersion. While agitating add the dispersion to the above oily phase. Heat together the water and the propylene glycol to 75°C. Add the solution to the above oily phase with agitation. Cool, with agitation, until the temperature reaches 30°C.

4. Topical Aerosol

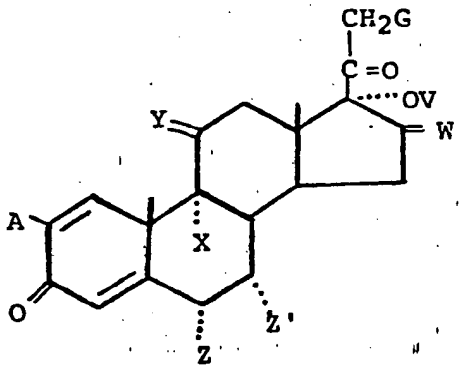
	mg/can
Active ingredient	6.4
Mineral Oil	1,250.0
Neobee M-5 (Caprylic/Capric Glyceride) (PVO International, Inc.)	3,743.6
Dichlorodifluoromethane	17,200.0
Trichloromonofluoromethane	68,800.0
	91,000.0

Dissolve the active ingredient in Neobee M-5 and add mineral oil. Place this concentrate into an aerosol and crimp a valve on the can. Inject the dichlorodifluoromethane and trichloromonofluoromethane mixture into the container through the valve.

The compounds of the general formula I are relatively non-toxic, at least not significantly more toxic than comparable 17 non-heterocyclic carboxylate derivatives corresponding to formula I such as betamethasone 17-valerate, with the ratio of potency to toxicity being generally better than betamethasone 17-valerate.

CLAIMS

1. 3,20-Dioxo-1,4-pregnadiene-17α-ol 17-aromatic heterocyclic carboxylates of the general formula I:



(I),

wherein A is hydrogen or, provided Y is (H,βOH), A may also be chloro, fluoro or methyl;

X is hydrogen or a halogen atom having an atomic weight less than 100;

Y is oxygen, (H,βOH) or, provided that X is hydrogen, Y may also be (H,H) or, provided X is chloro or bromo, Y may also be (H,β-halogen), the β-halogen having an atomic weight of less than 100 and being at least as electronegative as X;

Z is hydrogen, methyl, chloro or fluoro;

Z' is hydrogen or, provided that Z is hydrogen, may also be halogen having an atomic weight of less than 100;

V is an acyl radical of athiophenecarboxylic acid, pyrrole-carboxylic acid or furancarboxylic acid or the methyl- or halogen-substituted derivatives thereof;

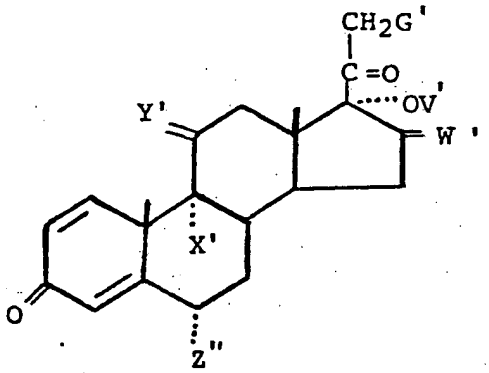
W is (H,H) , (H, loweralkyl) or (H, αOV_1) where V_1 is hydrogen or an acyl radical of retinoic acid or a carboxylic acid having up to 12 carbon atoms or W is =CHT where T is hydrogen, lower alkyl, fluoro or chloro and

G is hydrogen, a halogen atom having an atomic weight less than 100 or $-QV_2$ where Q is an oxygen or sulfur atom and V_2 is as defined for V or V_1 or is an acyl radical of phosphoric acid which may be in the form of a mono- or di-alkali metal or an alkaline earth metal salt thereof; and the 6-dehydro and 1,2-dihydro derivatives of the foregoing.

2. A compound as claimed in claim 1, characterised by being a 3,20-dioxo-1,4-pregnadiene.

3. A compound as claimed in claim 1 or claim 2, characterised in that V is furan-carbonyl or thiophenecarbonyl.

4. A compound as claimed in any one of claims 1 to 3, characterised by being of the general formula II:



(II),

where X' is fluoro or chloro;
Y' is (H,βOH) or, provided that X' is chloro, Y' may also be (H,β-halogen) the β-halogen having an atomic weight of less than 100 and being at least as electronegative as X';
Z" is hydrogen or fluoro;
W' is (H,H) or (H,CH_3);
V' is furan-carbonyl or thiophene-carbonyl; and
G' is chloro or fluoro or $-QV_2'$, where Q is an oxygen or sulfur atom (preferably oxygen) and V_2' is hydrogen or an acyl radical of retinoic acid, of a carboxylic acid having up to 12 (preferably up to 8) carbon atoms or of phosphoric acid which may be in the form of a mono- or di-alkali metal or alkaline earth metal salt.

5. A compound as claimed in claim 4, characterized in that G' is chloro, lower alkanoyloxy or lower alkoxy lower alkanoyloxy (preferably acetoxy or methoxyacetoxy), X' is chloro and Y' is (H,β-Cl) or X' is chloro or fluoro and Y' is (H,βOH) and W' is (H,H) or (H, CH_3), preferably (H, α-CH_3).

6. A compound as claimed in claim 1, said compound being selected from:

9α, 11β, 21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate);

9α, 11β, 21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-thenoate);

6α-fluoro-9α, 11β, 21-trichloro-16α-methyl-1,4-pregnadiene-17α-ol-3,20-dione 17-(2'-furoate);

9α-fluoro-16α-methyl-1,4-pregnadiene-11β, 17α, 21-triol-3,20-dione 17-(2'-furoate) 21-acetate;

9α-fluoro-16α-methyl-1,4-pregnadiene-11β, 17α,21-triol-3,20-dione 17-(2'-furoate) 21-methoxy-acetate;

9α-fluoro-16α-methyl-1,4-pregnadiene-11β, 17α, 21-triol-

3,20-dione 17-(2'-thenoate) 21-acetate;
9α-fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(3'-furoate) 21-acetate;
9α-fluoro-21-chloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-furoate);
9α-fluoro-21-chloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-thenoate);
9α,21-dichloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-furoate);
9α,21-dichloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione 17-(2'-thenoate);
9α-chloro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-acetate;
9α-chloro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-(2'-furoate) 21-methoxyacetate;
9α-fluoro-21-fluoro-16α-methyl-1,4-pregnadiene-11β,17α-diol--3,20-dione 17-(2'-furoate); and
9α-chloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-21-thiol--3,20-dione 17-(2'-furoate) 21-pivalate.

7. A process for the preparation of a 17α-aromatic heterocyclic carboxylate claimed in claim 1, said process being characterised in that an appropriate 3,20-dioxo-1,4-pregnadiene starting material, or a 6-dehydro- or 1,2-dihydro derivative thereof, is subjected to:

A: introduction of the desired ester group at the 16α,17α and/or 21 positions, or

B: hydrolysis of an ester group present at one or more of positions 11β,16α and 21 or of a 16α,17α-or 17α,21-ortho ester group, or

C: halogenation at one or more of positions 9α,11β and 21, or

D: reduction of an 11-oxo group to an 11β-hydroxy group.

8. A process as claimed in claim 7 process A, characterised by esterifying a 3,20-dioxo-1,4-pregnadiene-17α,21-

-diol 21-acylate otherwise corresponding to that of formula I wherein A and Z' are both hydrogen, X is chloro and Y is (H,β-Cl), or X is fluoro and Y is (H,β-OH), Z is hydrogen or fluoro, W is (H,CH_3) preferably (H,α-CH_3) and G is an acyloxy radical as defined in the definition of -QV_2, with a reactive derivative of furan- or thiophene-carboxylic acid.

9. A process as claimed in claim 7 process B, characterised by hydrolysing at position 21 a 17α-furoate 21-acylate or 17α-thenoate 21-acylate or a 17α,21-ortho ester, that is a 17α,21--alkyl-ortho-furoate or -thenoate, otherwise corresponding to that of formula I wherein A and Z' are both hydrogen, X and Y are as defined for formula I, Z is hydrogen or fluoro, and W is (H,CH_3),preferably (H,α-CH_3) and where desired re-esterifying at C-21 a so-obtained 17α,21-diol 17α-furoate or -thenoate to give another required 17α,21-diester of the general formula I.

10. A process as claimed in claim 7 process C, characterised by chlorinating at the C-21 position a 3,20-dioxo-1,4-pregnadiene 21-reactive acylate, such as 21-sulfonate, otherwise corresponding to that of the general formula I wherein A and Z' are both hydrogen, X is fluoro, Y is (H,β-OH), Z is hydrogen or fluoro, W is (H,CH_3) preferably (H,α-CH_3) and V is an acyl radical of furan- or thiophene-carboxylic acid, with a suitable source of chloride ion.

11. A process as claimed in claim 7 process C, characterised by addition of two chlorine atoms, or a 9α-chloro and 11β-hydroxy group, to the 9(11)-double bond of a 3,20-dioxo-1,4, 9(11)-pregnatriene otherwise corresponding to that of formula I wherein A and Z' are both hydrogen, Z is hydrogen or fluoro, W is (H,CH_3), preferably (H,α-CH_3), G is chloro, fluoro or an acyloxy radical as defined in the definition of -QV_2 and V is an acyl radical of furan- or thiophene-carboxylic acid to give the required 9α,11β-dichloro- and 9α-chloro-11β-hydroxy compounds of the general formula I, and where desired converting

a 21-acylate function into the corresponding 21-chloro function.

12. A process as claimed in claim 7 process C, characterised by ring opening of the 9β,11β-epoxide ring, with concomitant addition of HF or HCl, of a 9β,11β-oxido-3,20-dione-1,4-pregnadiene otherwise corresponding to that of the formula I wherein A and Z' are both hydrogen, Z is hydrogen or fluoro, W is (H,CH_3), preferably $(H,\alpha\text{-}CH_3)$, G is chloro, fluoro or an acyloxy radical as defined in the definition of $-QV_2$ and V is an acyl radical of furan- or thiophene-carboxylic acid to give the required 9α-chloro-11β-hydroxy- or 9α-fluoro-11β-hydroxy-compound of the general formula I.

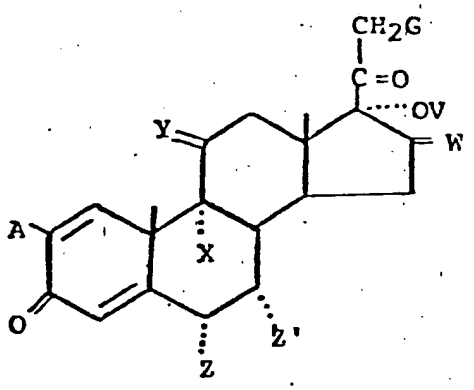
13. A process as claimed in claim 7 process D, characterised by reducing at the C-11 position a 3,11,20-trioxo-1,4-pregnadiene corresponding to that of the general formula I wherein A and Z' are both hydrogen, X is hydrogen or fluoro, Z is hydrogen or fluoro, W is (H,CH_3), preferably $(H,\alpha\text{-}CH_3)$, V is an acyl radical of furan- or thiophene-carboxylic acid and G is an acyloxy radical as defined in the definition of $-QV_2$.

14. A compound as claimed in any one of claims 1 to 6 for use as a pharmaceutical, especially for use as an anti-inflammatory.

15. A pharmaceutical composition, especially for use as an anti-inflammatory, comprising as active ingredient a compound as claimed in any one of claims 1 to 6 together with a suitable pharmaceutical carrier.

SPECIAL CLAIMS FOR AUSTRIA

1. A process for the preparation of 3,20-dioxo-1,4-pregnadiene-17α-ol 17 aromatic heterocyclic carboxylates of the general formula I:



(I),

wherein A is hydrogen or, provided Y is (H,βOH), A may also be chloro, fluoro or methyl;

X is hydrogen or a halogen atom having an atomic weight less than 100;

Y is oxygen, (H,βOH) or, provided that X is hydrogen, Y may also be (H,H) or, provided X is chloro or bromo, Y may also be (H,β-halogen), the β-halogen having an atomic weight of less than 100 and being at least as electronegative as X;

Z is hydrogen, methyl, chloro or fluoro;

Z' is hydrogen or, provided that Z is hydrogen, may also be halogen having an atomic weight of less than 100;

V is an acyl radical of a thiophenecarboxylic acid, pyrrolecarboxylic acid or furancarboxylic acid or the methyl or halogen-substituted derivatives thereof;

W is (H,H) , (H, loweralkyl) or (H, αOV_1) where V_1 is hydrogen or an acyl radical of retinoic acid or a carboxylic acid having up to 12 carbon atoms or W is =CHT where T is hydrogen, lower alkyl, fluoro or chloro and

G is hydrogen, a halogen atom having an atomic weight less than 100 or $-QV_2$ where Q is an oxygen or sulfur atom and V_2 is as defined for V or V_1 or is an acyl radical of phosphoric acid which may be in the form of a mono- or di-alkali metal or an alkaline earth metal salt thereof; and the 6-dehydro and 1,2-dihydro derivatives of the foregoing,

characterised by comprising one or more of the following processes A to D:

A: introduction of a desired ester group at one of more of positions 16α,17α and/or 21 of a starting material otherwise corresponding to that of the general formula I,

B: hydrolysis of an ester group present at one or more of positions 11β, 16α and 21 in a starting material otherwise corresponding to that of the general formula I,

C: halogenation at one or more of positions 9α,11β and 21 of a 9(11)-ene, a 9β,11β-epoxide or a 21-reactive acylate starting material to give a corresponding 9α,11β-dihalo, 9α-halo- 11β-hydroxy or 21-halo-compound of the general formula I, and

D: reduction at the 11-keto group of an 11-one starting material to give a corresponding 11β-hydroxy compound of the general formula I.

2. A process as claimed in claim 1 process A, characterised by esterifying a 3,20-dioxo-1,4-pregnadiene 17α,21-diol 21-acylate/otherwise corresponding to that of formula I wherein A and Z' are

both hydrogen, X is chloro and Y is (H,β-Cl), or X is fluoro and Y is (H,β-OH), Z is hydrogen or fluoro, W is (H,CH_3), preferably (H,α-OH_3), and G is an acyloxy radical as defined in the definition of -QV_2, with a reactive derivative of furan- or thiophene-carboxylic acid.

3. A process as claimed in claim 1 process B, characterised by hydrolysing at position 21 a 17α-furoate-21-acylate or 17α-thenoate-21-acylate or a 17α,21-ortho ester, that is a 17α,21--alkyl-ortho-furoate or -thenoate, otherwise corresponding to that of formula I wherein A and Z' are both hydrogen, X and Y are as defined for formula I, Z is hydrogen or fluoro, and W is (H,CH_3) preferably (H,α-CH_3), and where desired re-esterifiying at C-21 a so-obtained 17α,21-diol 17α-furoate or -thenoate to give another required 17α,21-diester of the general formula I.

4. A process as claimed in claim 1 process C, characterised by chlorinating at the C-21 position a 3,20-dioxo-1,4-pregnadiene 21-reactive acylate, such as 21-sulfonate, otherwise corresponding to that of the general formula I wherein A and Z' are both hydrogen, X is fluoro, Y is (H,β-OH), Z is hydrogen or fluoro, W is (H,CH_3), preferably (H,β-OH), and V is an acyl radical of furan- or thiophene-carboxylic acid, with a suitable source of chloride ion.

5. A process as claimed in claim 1 process C, characterised by addition of two chlorine atoms, or a 9α-chloro and 11β-hydroxy group, to the 9(11)-double bond of a 3,20-dioxo-1,4,9(11)-pregnatriene otherwise corresponding to that of formula I wherein A and Z' are both hydrogen, Z is hydrogen or fluoro, W is (H,CH_3) preferably (H,α-CH_3), G is chloro, fluoro or an acyloxy radical as defined in the definition of -QV_2 and V is an acyl radical of furan- or thiophene-carboxylic acid to give the required 9α,11β-dichloro- and 9α-chloro-11β-hydroxy compounds of the general formula I, and where desired converting a 21-acylate function into the corresponding 21-chloro function.

6. A process as claimed in claim 1 process C, characterised by ring opening of the 9β,11β-epoxide ring, with concomitant addition of HF or HCl of a 9β,11β-oxido-3,20-dione-1,4--pregnadiene otherwise corresponding to that of the formula I wherein A and Z' are both hydrogen, Z is hydrogen or fluoro, W is (H,CH_3), preferably $(H,\alpha CH_3)$, G is chloro, fluoro or an acyloxy radical as defined in the definition of $-QV_2$ and V is an acyl radical of furan- or thiophene-carboxylic acid to give the required 9α-chloro-11β-hydroxy- or 9α-fluoro-11β-hydroxy-compound of the general formula I.

7. A process as claimed in claim 1 process D, characterised by reducing at the C-11 position a 3,11,20-trioxo-1,4-pregnadiene corresponding to that of the general formula I wherein A and Z' are both hydrogen, X is hydrogen or fluoro, Z is hydrogen or fluoro, W is (H,CH_3), preferably $(H,\alpha\text{-}CH_3)$, V is an acyl radical of furan- or thiophene-carboxylic acid and G is an acyloxy radical as defined in the definition of $-QV_2$.

8. A process as claimed in claim 1 process B, characterised by hydrolysing at position 11 an 11β-protected-hydroxy-17α--furoate- (or 17α-thenoate)-21-acylate otherwise corresponding to that of formula I wherein A and Z' are both hydrogen, X is halogen preferably fluoro, Z is hydrogen or fluoro, W is (H,CH_3) preferably $(H,\alpha\text{-}CH_3)$ and the 21-acylate is the group $-QV_2$ where Q and V_2 are as defined for formula I to give the corresponding 11β-free hydroxy-17α,21-diester of the general formula I.

9. A process for the preparation of a pharmaceutical composition with comprises admixing a compound of the general formula I set forth in claim 1 with a suitable pharmaceutically acceptable carrier.

10. A process as claimed in claim 9, wherein the compound of the general formula I set forth in claim 1 has been prepared by a process as claimed in any one of claims 1 - 8.

European Patent Office

EUROPEAN SEARCH REPORT

Application number
EP 82 10 0490

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	DE - B - 1 059 906 (SCHERICO LTD) * Column 46, example 40 *	1
A	GB - A - 1 191 965 (WARNER LAMBERT) * Claim 1, pages 1,2 *	1,14, 15
A	US - A - 4 221 787 (NICHOLAS S. BODOR) * Claims 1,7,85,86 *	1,14, 15
A	DE - A - 2 031 205 (WARNER LAMBERT) * Claims 1,14,15,21-23, pages 6, 7 *	1,14, 15
A	ARZNEIMITTEL FORSCHUNG, vol.29, no.11, november 1979 AULENDORF (DE) B.N. LUTSKY et al.: "A Novel Class of Potent Topical Antiinflammatory Agents: 17-Benzoylated, 7 -Halogeno Substituted Corticosteroids" pages 1662-1667 * The whole document *	1,14, 15

CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
C 07 J 17/00
C 07 J 33/00
C 07 J 43/00
A 61 K 31/58

TECHNICAL FIELDS SEARCHED (Int.Cl. 3)
C 07 J 17/00
C 07 J 33/00
C 07 J 43/00

CATEGORY OF CITED DOCUMENTS
X: particularly relevant if taken alone
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A: technological background
O. non-written disclosure
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E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons
&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	22-04-1982	HENRY

EPO Form 1503.1 06.78